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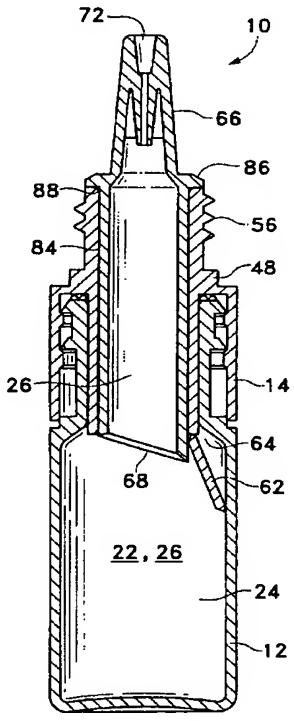
(54) Pharmaceutical container with two seperate, unstable substances

(57) A device (10) for the delivery of unstable pharmaceutical preparations is disclosed. The device includes an upper container (14) for receiving a first component of the preparation and a lower container (12) for receiving a second component of the preparation. The first and second components are unstable when mixed. Advantageous preparations for use in the device are also disclosed.

FIG. 10



Description

Field of the Invention

[0001] The present invention generally pertains to the delivery of unstable liquids. More particularly, but not by way of limitation, the present invention pertains to the delivery of unstable pharmaceutical preparations to the eye, ear, or nose.

Description of the Related Art

[0002] Topical pharmaceutical preparations for the eye, ear, and nose are typically formulated as a liquid solution or suspension. However, certain topical preparations have individual components that, if mixed, have a shelf life of only a few weeks. Typically, one of the components is in a powdered form, and the other component is in a liquid form. Such topical pharmaceutical preparations were initially packaged with the unstable components in two separate containers. The components were then dispensed in certain specified amounts from their separate containers into a third container and mixed just prior to delivery. Delivery of the mixed preparation was typically accomplished via a conventional dropper. Because of the inconvenience of and the risk of user non-compliance with such two container preparations, various containers were developed having two, separate compartments for the unstable components. Such containers could be manipulated by a user to mix the components just prior to delivery and then deliver the mixed preparation via an integrated nozzle. U.S. Patent Nos. 5,474,209 and 5,782,345, provide examples of such containers.

[0003] However, a need still exists in the pharmaceutical industry for an effective means of delivering unstable pharmaceutical preparations to the eye, ear, and nose. The present invention provides advantageous devices and formulations to meet this need.

Summary of the Invention

[0004] One aspect of the present invention is a device for the delivery of a pharmaceutical preparation having a first component and a second component. The device includes an upper container for receiving the first component and having a bottom. The first component includes an unstable anti-infective agent. The device also includes a lower container for receiving a second component. The second component includes a liquid carrier for the first component. The device further includes a tubular sleeve movably disposed within the upper container and a cap rotationally coupled to the upper container. When the cap is screwed onto the upper container, the tubular sleeve tears the bottom of the upper container to place the first component in communication with the second component.

[0005] In another aspect, the device includes an upper container for receiving a first component and having a bottom. The first component includes a first pharmaceutically active agent. The device also includes a lower container for receiving a second component unstable in the first component. The second component includes a second pharmaceutically active agent. The device further includes a tubular sleeve movably disposed within the upper container and a cap rotationally coupled to the upper container. When the cap is screwed onto the upper container, the tubular sleeve tears the bottom of the upper container to place the first component in communication with the second component.

Brief Description of the Drawings

[0006] For a more complete understanding of the present invention, and for further objects and advantages thereof, reference is made to the following description taken in conjunction with the accompanying drawings in which:

FIG. 1 is an exploded view of a device for the delivery of unstable pharmaceutical preparations according to a preferred embodiment of the present invention;
FIG. 2 is a cross-sectional view of FIG. 1;
FIG. 3 is a front view of the device of FIG. 1 in the assembled state in which the unstable components of the pharmaceutical preparation are not mixed;
FIG. 4 is a cross-sectional view of FIG. 3;
FIG. 5 is an enlarged, cross-sectional view of the upper container of the device of FIG. 1;
FIG. 6 is a sectional view of FIG. 5 taken along line 6-6;
FIG. 7 is a top view of the safety ring of the device of FIG 1;
FIG. 8 is an exploded, cross-sectional, fragmentary view of the tubular sleeve, upper container, and cap of the device of FIG. 1;
FIG. 9 is a front view of the device of FIG. 1 in the assembled state in which the unstable components of the pharmaceutical preparation have been mixed, the cap is removed, and the device is ready to dispense the mixed pharmaceutical preparation; and
FIG. 10 is a cross-sectional, fragmentary view of FIG. 9.

Detailed Description of Preferred Embodiments

[0007] The preferred embodiments of the present invention and their advantages are best understood by referring to FIGS. 1-10 of the drawings, like numerals being used for like and corresponding parts of the various drawings.

[0008] Referring generally to FIGS. 1-8, a device 10 for the delivery of unstable liquids is shown according to a preferred embodiment of the present invention. De-

vice 10 is preferably used to deliver topical pharmaceutical preparations to the eye, car, or nose. For ease of description but not by way of limitation, device 10 is described hereinafter as a device for the delivery of topical pharmaceutical preparations.

[0009] As shown best in the exploded views of FIGS. 1-2, device 10 generally includes a lower container 12, and upper container 14, a tubular sleeve or member 16, a cap 18, and a safety seal 19. As shown best in FIGS. 3 and 4, in the assembled state of device 10, upper container 14 is coupled to lower container 12, tubular sleeve 16 is disposed within and coupled to upper container 14, cap 18 covers tubular sleeve 16 and is removably coupled to upper container 14, and safety seal 19 is disposed around upper container 14 below cap 18. Cap 18 and safety seal 19 are shown in dashed lines in FIG. 4 for clarity of illustration. The various portions of device 10 are preferably formed from conventional polymeric materials. Most preferably, lower container 12 is formed of low density polyethylene, upper container 14 is formed of high density polyethylene, tubular sleeve 16 is formed of Zylar, a copolymer available from NOVA Chemicals of Leominster, Massachusetts, and cap 18 is formed of polypropylene. Upper container 14 has a reservoir 20 for holding a first component 22 of a pharmaceutical preparation. Lower container 12 has a reservoir 24 for holding a second component 26 of a pharmaceutical preparation. When mixed, first component 22 is unstable in second component 26 after a certain time period, which may be as long as several weeks or months, or as short as a few hours or minutes.

[0010] Lower container 12 includes a hollow neck 28 that includes two ring shaped edges 30 and 32. Stria 34 are located on edges 30 and 32. A shoulder 36 is located at the junction of neck 28 and reservoir 24. Sealing rings 37 are located on the internal surface of neck 28 above shoulder 36.

[0011] As shown best in FIGS. 2 and 4, upper container 14 includes a surface 82 that mates with sealing rings 37 of lower container 12 to prevent leakage of second component 26 from reservoir 24 or entry of air into reservoir 24. Upper container 14 also includes a flap 38 that surrounds neck 28 of lower container 12. As shown best in FIG. 5, flap 38 includes two ring shaped ribs 40 and 42 disposed on the internal surface 44 of flap 38 and for mating with edges 30 and 32 of lower container 12. Stria 46 run vertically along internal surface 44 from rib 40 to the internal surface of shoulder 48. Although not shown in the FIGS., stria 46 also run horizontally and radially along the internal surface of shoulder 48 toward the longitudinal axis of upper container 14. When upper container 14 is disposed on lower container 12, stria 34 of edges 30 and 32 couple with stria 46 to prevent upper container 14 and lower container 12 from rotating relative to each other. As shown best in FIGS. 5-6, a plurality of sawteeth 50 are disposed on the external surface of shoulder 48. As shown in FIG. 7, sawteeth 50 mate with flexible wings 52 to removably couple safety seal 19 to upper container 14. Safety seal 19 has a ring-shaped geometry with a perforation at connecting point 58. Safety seal 19 has an axial wing 56 that is connected to the remainder of seal 19 at a connecting point 59. Upper container 14 also has a neck 55 having external threads 56 for mating with internal threads 60 of cap 18, as is best shown in FIG. 8. As is best shown in FIG. 5, upper container 14 has bottom 62 that is tearable along a perforated line 64 disposed about the periphery of bottom 62.

[0012] Tubular sleeve 16 includes a hollow body 64 having a truncated cone-shaped portion 66 on one end and a helicoidal edge 68 on an opposite end. Truncated cone-shaped portion 66 has a internal channel 70 terminating in a reverse truncated cone-shaped hole 72 that serves as the nozzle or dropper to dispense a pharmaceutical preparation from device 10. Alternatively truncated cone-shaped portion 66 may be modified to include a conventional "Luer Lok" that complies with Luer Taper Specification 70.1 of the American Standards Association and that allows coupling to a syringe, cannula, or other conventional medical instruments. Helicoidal edge 68 preferably has a small horizontal section 74. Tubular sleeve 16 also includes a first sealing ring 76 and a second sealing ring 78 disposed on the external surface of body 64. Sealing rings 76 and 78 mate with internal surface 84 of reservoir 20 of upper container 14 to prevent leakage of first component 22 from reservoir 20 or entry of air into reservoir 20. Sealing ring 78 is especially useful in preventing such leakage or entry when first component 22 is a liquid. As shown in FIG. 8, cap 18 preferably has a member 80 that seals hole 72 when cap 18 is screwed onto upper container 14.

[0013] The above-referenced description is a summary of the structure of device 10. Certain portions of device 10 are described in greater detail in U.S. Patent Nos. 5,474,209 and 5,782,345.

[0014] As mentioned hereinabove, reservoir 20 of upper container 14 holds first component 22 of a pharmaceutical preparation. Reservoir 24 of lower container 12 holds a second component 26 of a pharmaceutical preparation. Alternatively, first component 22 and second component 26 may be the unstable components of a liquid other than a pharmaceutical preparation.

[0015] First component 22 preferably comprises an ophthalmically effective amount of one or more pharmaceutically active agents, or an otorhinolaryngologically effective amount of one or more pharmaceutically active agents. First component 22 may also comprise an ophthalmically acceptable carrier or an otorhinolaryngologically acceptable carrier, respectively. As used herein, "ophthalmically acceptable carrier" refers to any substance or combination of substances that are non-reactive with the pharmaceutically active agent and suitable for administration to a user's eye. As used herein, "otorhinolaryngologically acceptable carrier" refers to any substance or combination of substances that are non-reactive with the pharmaceutically active agent and

suitable for administration to a user's ear or nose. Solubilizers and stabilizers are deemed to be non-reactive. By way of example, an ophthalmically acceptable carrier or an otorhinolaryngologically acceptable carrier may comprise any combination of preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, solubilizers, stabilizers, pH adjusters, tonicity agents, fillers, and water. Preferred pharmaceutically active agents are anti-infectives, including, without limitation, antibiotics, antivirals, and antifungals; steroidal and non-steroidal anti-inflammatory agents; and combinations of the foregoing. Preferred antibiotics include, without limitation, trimcthoprims; polymyxin B sulfate; beta-lactams, including, without limitation, cephalosporins, penicillins, thienamycins, penems, cephems, and trinems; oxazolidinones; macrolides, including without limitation, erythromycins and erythromycin lactobionate; keytolides; tetracyclines, including, without limitation, chlortetracylcines and chlortetracycline hydrochloride; and pristinomycins. Preferred steroidal anti-inflammatory agents include, without limitation, dexamethasone and dexamethasone phosphate. First component 22 may be in a powder or liquid form.

[0016] Second component 26 preferably comprises an ophthalmically effective amount of one or more pharmaceutically active agents, or an otorhinolaryngologically effective amount of one or more pharmaceutically active agents. Second component 26 may also comprise an ophthalmically acceptable carrier or an otorhinolaryngologically acceptable carrier, respectively. Second component 26 preferably utilizes the same preferred pharmaceutically active agents as first component 22. Alternatively, second component 26 may comprise an ophthalmically or otorhinolaryngologically acceptable carrier but no pharmaceutically active agent. In this case, second component 26 acts as a diluent to first component 22. Still further in the alternative, first component 22 may comprise an ophthalmically or otorhinolaryngologically acceptable carrier but no pharmaceutically active agent, and second component 26 may comprise one or more pharmaceutically active agents. In this case, first component 22 acts as a diluent for second component 26.

[0017] The above-described portions of device 10, including components 22 and 26 of a pharmaceutical preparation, are assembled using conventional techniques. Device 10 is preferably sterilized by conventional ganuna radiation methods if such methods do not inhibit the efficacy of the pharmaceutical preparation. Alternatively, device 10 may be sterilized by conventional Eto methods, if necessary.

[0018] Referring generally to FIGS. 1-10, the preferred use of device 10 to mix components 22 and 26 of a pharmaceutical preparation and dispense the preparation into the eye, ear, or nose of a user will now be described in greater detail. As shown in FIGS. 3-4, device 10 is in a first position in which components 22 and 26 are unmixed. To mix components 22 and 26, a user first moves axial wing 56 of safety seal 19 radially outward, breaking connecting point 59. The user then holds axial wing 56 and rotates safety seal 19 about a longitudinal axis of device 10, causing sawteeth 50 of upper container 14 to engage flexible wings 52 of safety seal 19. Such rotation splits safety seal 19 at connection point 58. The user can then remove safety seal 19 from device 10.

[0019] Next, the user screws cap 18 downward onto neck 55 of upper container 14. During this downward travel of cap 18, internal shoulder 85 of cap 18 contacts external shoulder 86 of tubular sleeve 16. Tubular sleeve is pushed downward within upper container 14 until external shoulder 86 of tubular sleeve 16 contacts shoulder 88 of upper container 14. Referring to FIG. 10, as tubular sleeve 16 is pushed downward, helicoidal edge 68 tears bottom 62 of reservoir 22 along perforation 64, with the exception of a portion of perforation 64 at horizontal section 74 of edge 68. Bottom 62 is thus opened but remains connected to upper container 14. First component 22 is then in communication with second component 26, and may be further mixed by shaking device 10, if necessary. In this second position of device 10 in which components 22 and 26 are mixed, sealing rings 76 and 78 mate with internal surface 84 of upper container 14 to prevent leakage of the components from reservoirs 20 and 24 or entry of air into the reservoirs. Upon removal of cap 18, the mixed pharmaceutical preparation may be dispensed into the eye, ear, or nose of a user by squeezing on the external surface of lower container 12 so as to force the mixture through nozzle 66 of tubular sleeve 16. When cap 18 is rethreaded onto tubular sleeve 16, member 80 seals hole 72.

[0020] The following examples illustrate advantageous pharmaceutical preparations suitable for delivery with the device of the present invention, but are in no way limiting.

EXAMPLE 1

[0021] Device 10 may be used to deliver an ophthalmic or otic pharmaceutical preparation comprising a first component 22 that is a solution having dexamethasone phosphate as a pharmaceutically active agent and a second component 26 that is a solution having both trimethoprim and polymyxin B sulfate as pharmaceutically active agents. First component 22 preferably has a volume of 1 ml. The composition of first component 22 is 0.5 % weight/volume dexamethasone phosphate, 0.01 % weight/volume benzalkonium chloride, 0.25 % weight/volume polysorbate 80, 12.20 % weight/volume trisodium citrate $2H_2O$, a quantity of citrate acid sufficient to adjust the pH of first component 22 to 7.8, and a quantity of water sufficient to adjust the volume of first component 22 to 100%. Second component 26 preferably has a volume of 4 ml. The composition of second component 26 is 0.125 % weight/volume trimethoprim,

1.25 mill. I.U. (per 100ml) polymyxin B sulfate, 0.01 % weight/volume benzalkonium chloride, 1.226 % weight/volume sulfuric acid 25%, 0.023 % weight/volume sodium chloride, a quantity of sodium hydroxide sufficient to adjust the pH of second component 26 to 5.7, and a quantity of purified water sufficient to adjust the volume of second component 26 to 100%. When packaged as described hereinabove in device 10 as shown in FIG. 4, first component 22 and second component 26 exhibit good stability results for up to twenty-four months. When first component 22 and second component 26 are mixed in device 10 via the tearing of bottom 62 of reservoir 20, an effective antibiotic/steroid pharmaceutical preparation may be delivered to the eye or the ear.

EXAMPLE 2

[0022] Device 10 may be used to deliver an ophthalmic pharmaceutical preparation comprising a first component 22 that is a powder having chlortetracycline hydrochloride as a pharmaceutically active agent and a second component 26 that acts as a ophthalmically acceptable carrier for first component 22. First component 22 preferably has a weight of 100 mg. The composition of first component 22 is 25 % weight/weight chlortetracycline hydrochloride and a quantity of lactose sufficient to adjust the weight of first component 22 to 100%. The exact quantity of lactose may vary slightly according to the potency of the chlortetracycline hydrochloride. Second component 26 preferably has a volume of 5 ml. The composition of second component 26 is 0.03 % weight/volume nipagin M, 0.02 % weight/volume nipasol M, 0.54 % weight/volume sodium chloride, 0.75 % weight/volume sodium tetraborate 10 H_2O, 0.2 % weight/volume polyvinylpyrrolidone, and a quantity of purified water sufficient to adjust the volume of second component 26 to 100 %. When packaged as described hereinabove in device 10 as shown in FIG. 4, first component 22 and second component 26 exhibit good stability results for up to twenty-four months. When first component 22 and second component 26 are mixed in device 10 via the tearing of bottom 62 of reservoir 20, an effective antibiotic pharmaceutical preparation may be delivered to the eye.

EXAMPLE 3

[0023] Device 10 may be used to deliver an ophthalmic pharmaceutical preparation comprising a first component 22 that is a powder having erythromycin lactobionate as a pharmaceutically active agent and a second component 26 that acts as a ophthalmically acceptable carrier for first component 22. First component 22 contains 50 mg of erythromycin lactobionate. Second component 26 preferably has a volume of 5 ml. The composition of second component 26 is 0.050 % weight/volume polysorbate 80, 3 % weight/volume sodium citrate 2 H_2O, 0.005 % weight/volume benzalkonium chloride, and a quantity of citric acid (pH 8.2) sufficient to adjust the volume of second component 26 to 100 %. When packaged as described hereinabove in device 10 as shown in FIG. 4, first component 22 and second component 26 exhibit good stability results for up to twenty-four months. When first component 22 and second component 26 are mixed in device 10 via the tearing of bottom 62 of reservoir 20, an effective antibiotic pharmaceutical preparation may be delivered to the eye. The polysorbate 80 contained in second component 26 avoids or minimizes benzalkonium chloride instability due to gamma radiation sterilization and advantageously allows device 10 to be sterilized by conventional gamma radiation methods instead of Eto methods.

[0024] The present invention is illustrated herein by example, and various modifications may be made by a person of ordinary skill in the art. For example, the geometries of the device and its individual components may be modified from the geometries described for the preferred embodiments. As another example, the device may be used with unstable pharmaceutically active agents other than anti-infectives and anti-inflammatories, or with other unstable liquids.

[0025] It is believed that the operation and construction of the present invention will be apparent from the foregoing description. While the apparatus, methods, and compositions shown or described above have been characterized as being preferred, various changes and modifications may be made therein without departing from the scope of the invention as defined in the following claims.

Claims

1. A device (10) for the delivery of an unstable pharmaceutical preparation having a first component and a second component, said first and second components being unstable when admixed,
in combination with a measured amount of said first component, and a measured amount of said second component, separately stored in said device prior to delivery,
wherein said device comprises:

an upper container (14) for receiving said first component and having a bottom (62),

a lower container (12) for receiving said second component,

a tubular sleeve (16) movably disposed within said upper container (14),

a cap (18) rotationally coupled to said upper container,

such that when said cap is screwed onto said

upper container, said tubular sleeve is urged to move within said upper container and is adapted to bear on and to tear said bottom of said upper container to place said first component in communication with said second component,

and wherein said first component comprises:
an anti-infective agent,
and wherein said second component comprises:
a liquid carrier for said first component.

2. The combination of claim 1, wherein said first component comprises a liquid.

3. The combination of claim 1, wherein said first component comprises a powder.

4. The combination of claim 1, wherein said liquid carrier comprises a pharmaceutically active agent.

5. The combination of any one of claims 1 to 4, wherein said second component comprises polysorbate 80 and benzalkonium chloride, and wherein said polysorbate 80 minimizes any instability of said benzalkonium chloride due to gamma radiation and allows said device to be sterilized by gamma radiation.

6. The combination of claim 1, wherein said anti-infective agent comprises an antibiotic selected from the group consisting of trimethoprims, polymyxin B sulfate, beta-lactams, oxazolidinones, macrolides, keytolides, tetracyclines, and pristinomycins.

7. A device (10) for the delivery of an unstable pharmaceutical preparation having a first component and a second component, said first and second components being unstable when admixed,
in combination with a measured amount of said first component, and a measured amount of said second component, separately stored in said device prior to delivery,
wherein said device comprises:

an upper container (14) for receiving said first component and having a bottom (62),

a lower container (12) for receiving said second component,

a tubular sleeve (16) movably disposed within said upper container (14),

a cap (18) rotationally coupled to said upper container,

such that when said cap is screwed onto said upper container, said tubular sleeve is urged to move within said upper container and is adapted to bear on and to tear said bottom of said upper container to place said first component in communication with said second component,

and wherein said first component comprises:
a first pharmaceutically active agent,
and wherein said second component comprises:
a second pharmaceutically active agent.

8. The combination of claim 7, wherein one of said pharmaceutically active agents comprises an anti-inflammatory agent, and the other of said pharmaceutically active agent comprises an anti-infective agent.

9. The combination of claim 7, wherein said first component and said second component are liquids.

10. The combination of claim 7, wherein one of said components is a liquid and the other of said components is a powder.

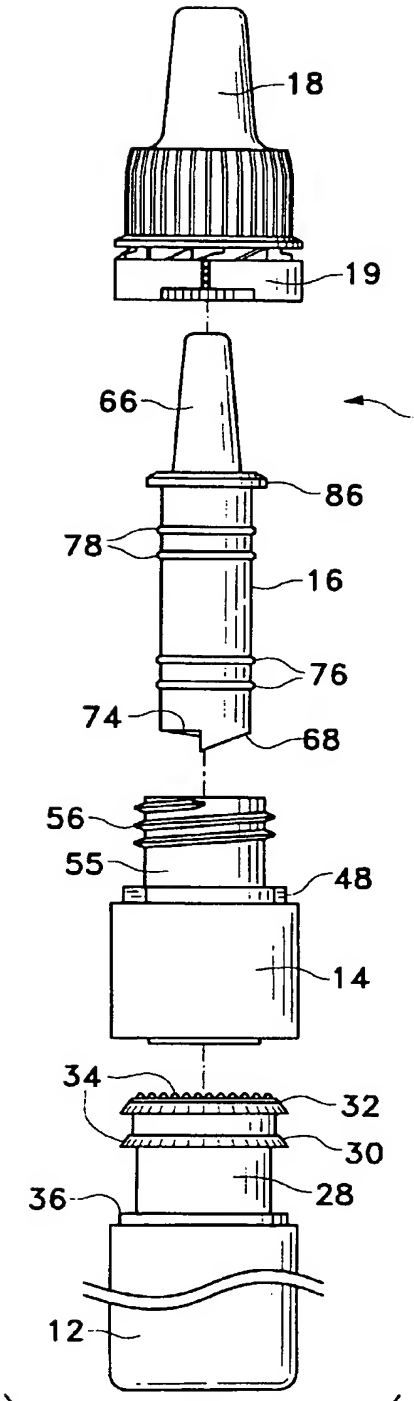

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FIG. 1

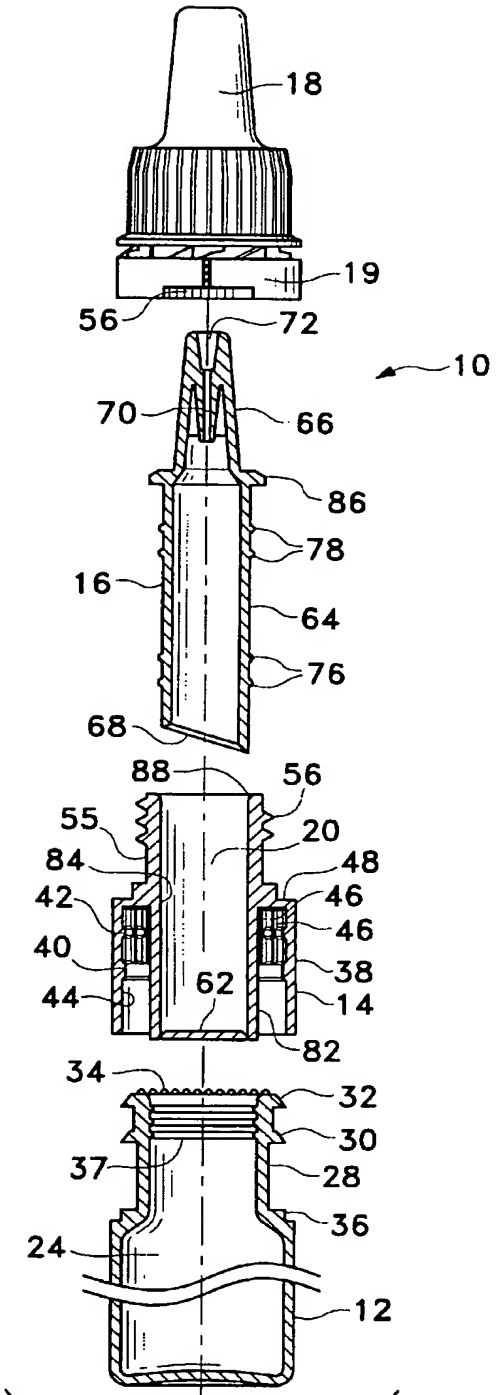
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FIG. 2

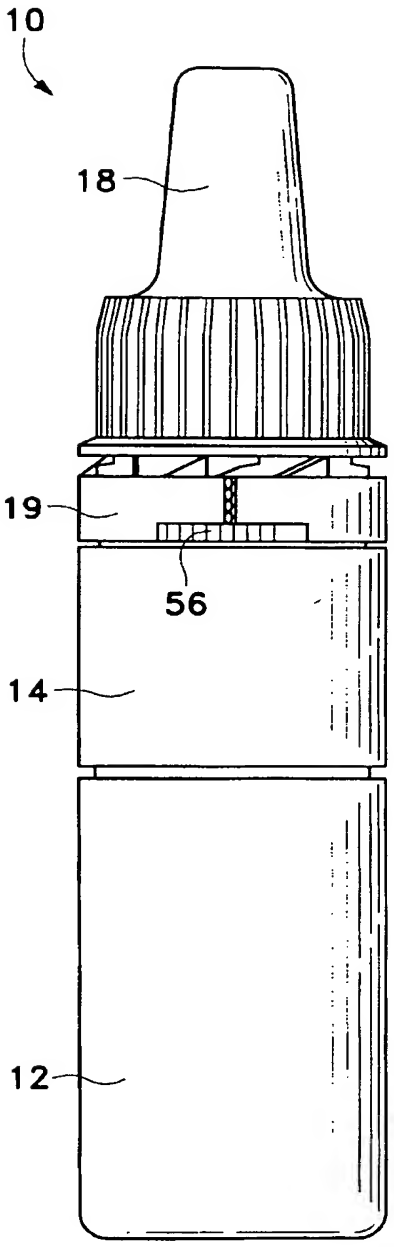

FIG. 3

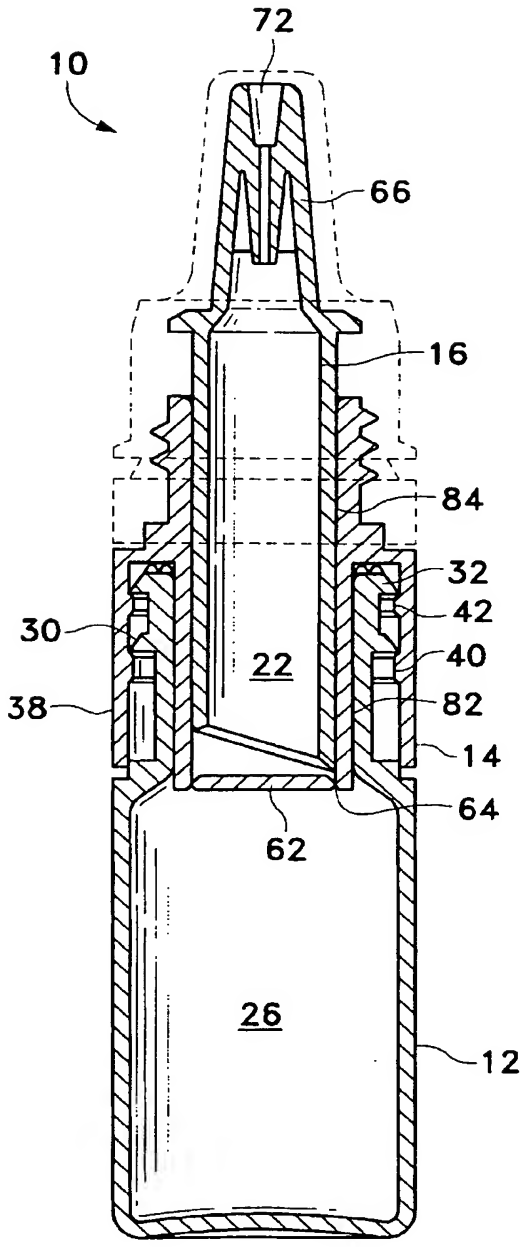

FIG. 4

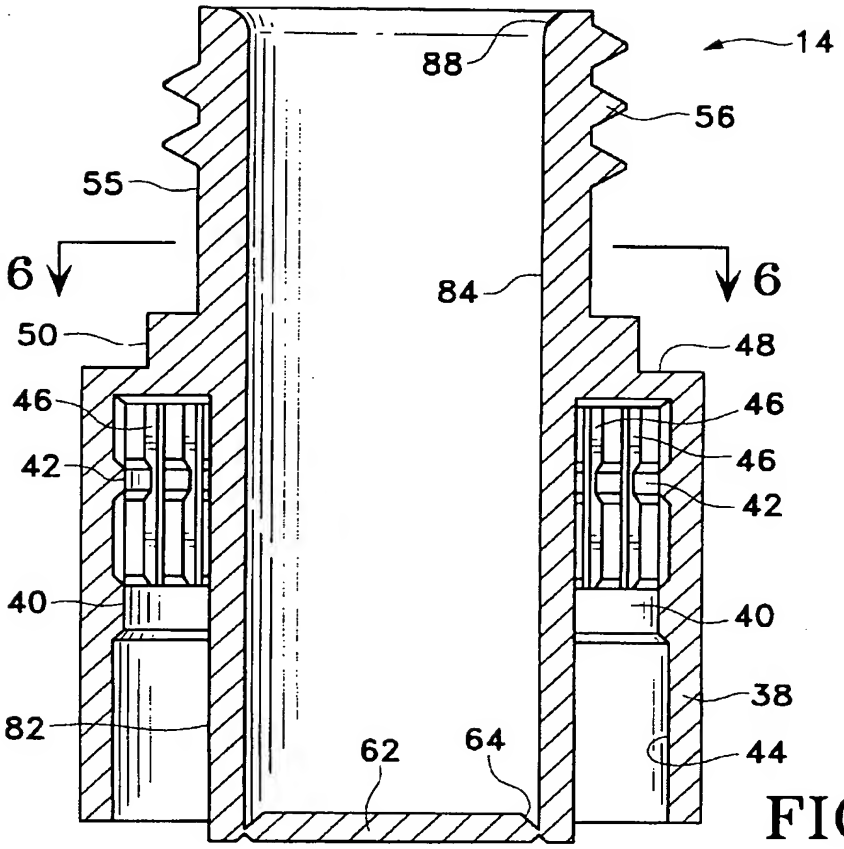
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FIG. 5

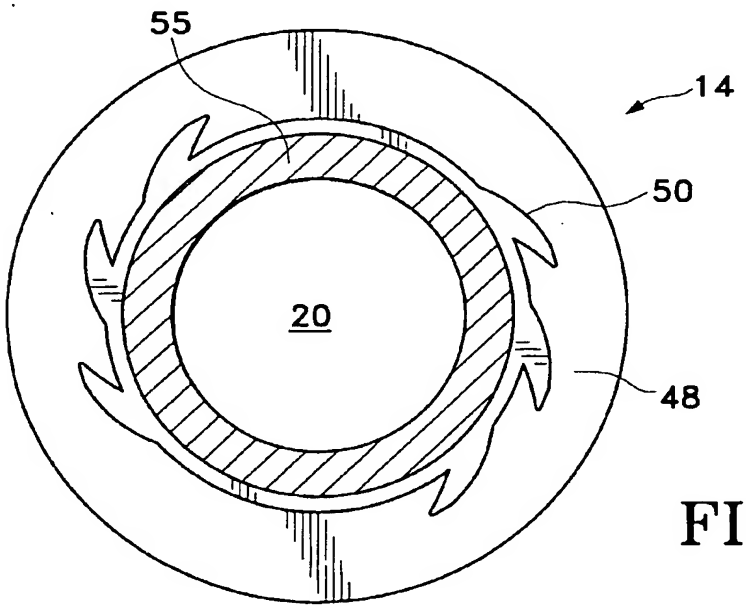
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FIG. 6

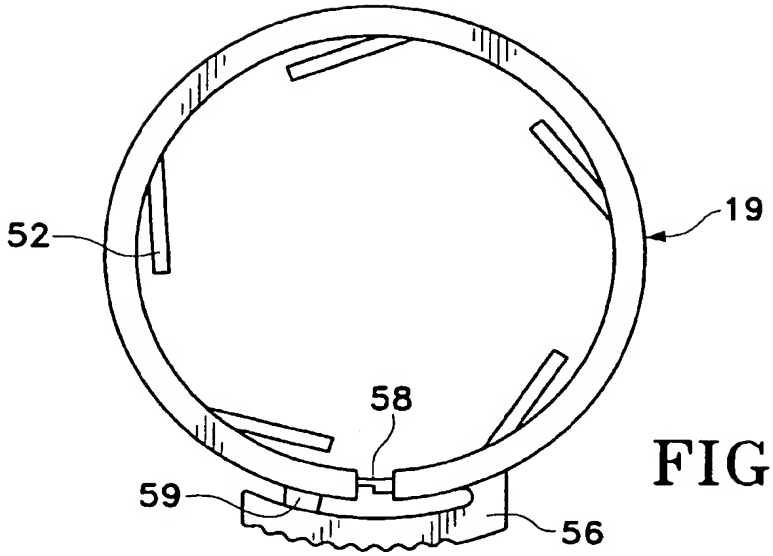

FIG. 7

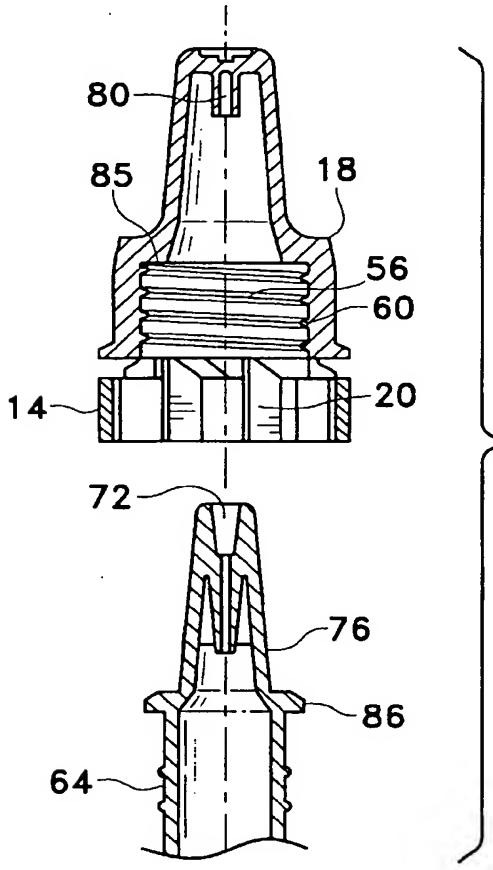

FIG. 8

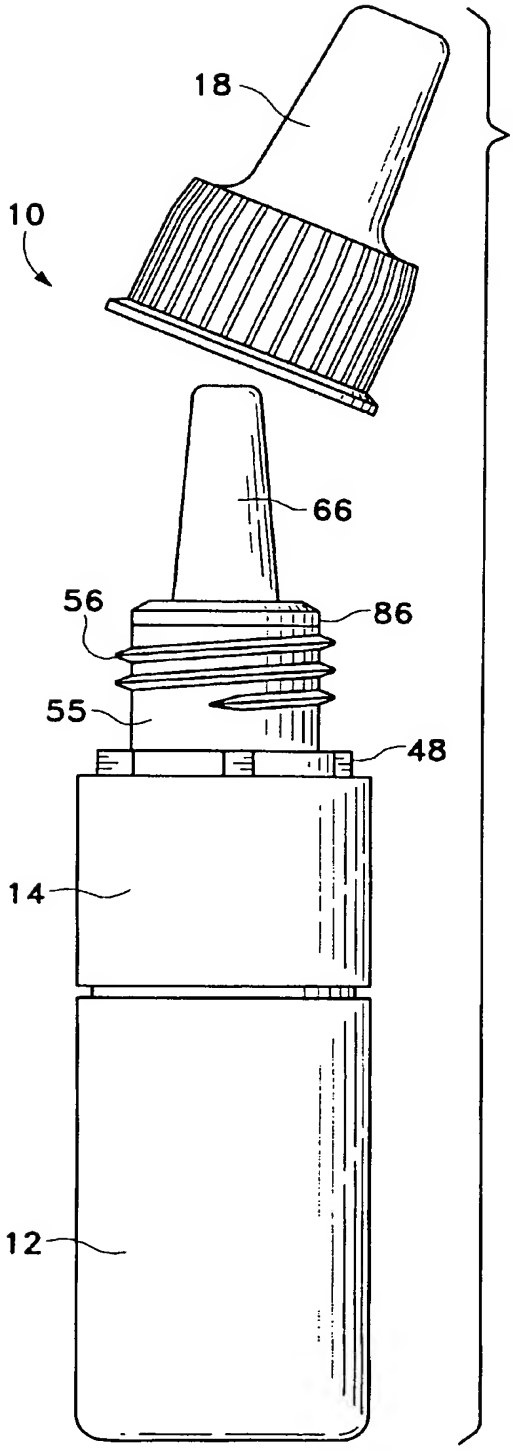
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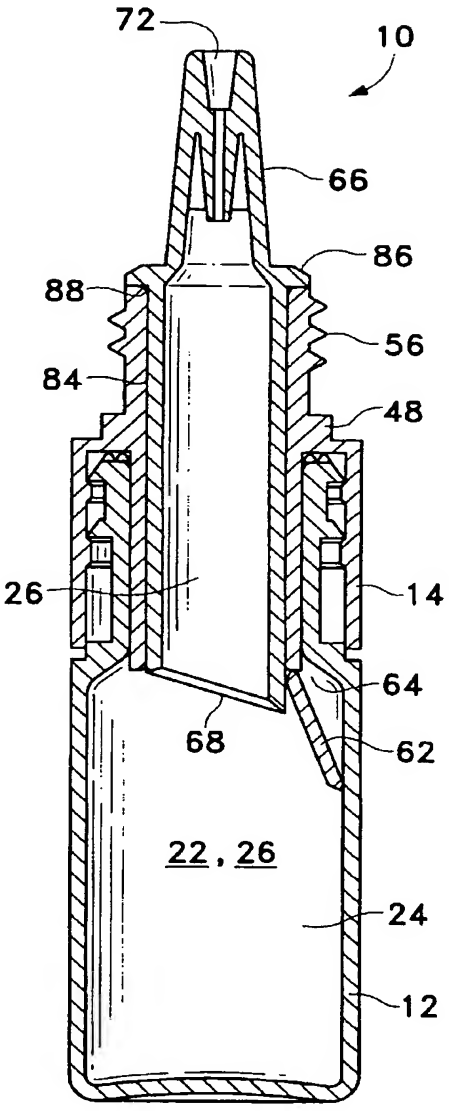
FIG. 9

FIG. 10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European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 00 20 4366

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
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TECHNICAL FIELDS SEARCHED (Int.Cl.7)

B65D
A61J
A61F

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	12 June 2001	Gino, C

CATEGORY OF CITED DOCUMENTS

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EPO FORM 1503 03.82 (P04C01)

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12-06-2001

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